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(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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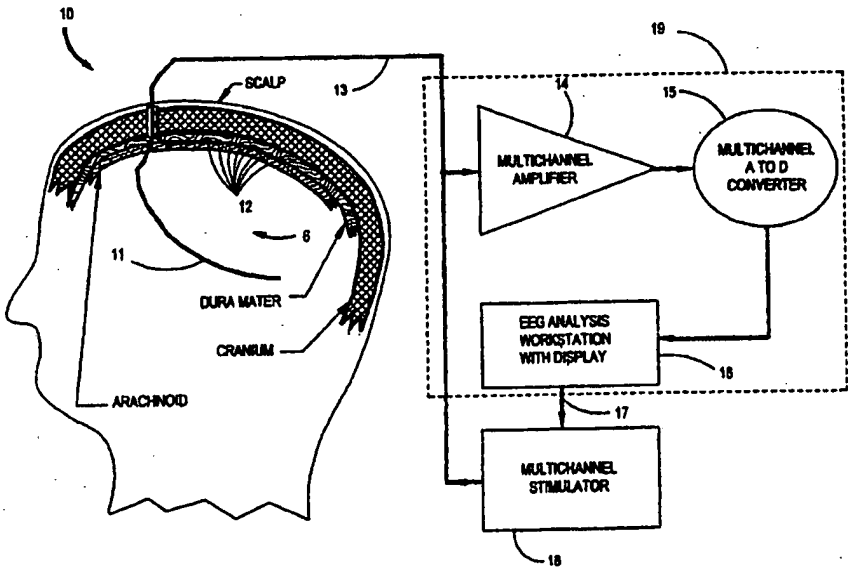
(54) Title: SYSTEM AND METHOD FOR DETERMINING STIMULATION PARAMETERS FOR THE TREATMENT OF EPILEPTIC SEIZURES



(57) Abstract: A method for selecting electrical stimulation parameters for controlling epileptiform activity in a patient includes implanting brain electrodes (6, 11, 12) in the patient, connecting the brain electrodes to an EEG analysis system (19) including a display workstation (16) and a stimulator (18), and collecting and analyzing EEG signals to determine whether electrical stimulation applied via the stimulator is effective to initiate or terminate epileptiform activity. If not, parameters are adjusted and stimulation, collection, and analysis steps are repeated.

WO 02/38031 A2

SYSTEM AND METHOD FOR DETERMINING STIMULATION PARAMETERS FOR THE TREATMENT OF EPILEPTIC SEIZURES

FIELD OF THE INVENTION

This invention is in the field of devices for the treatment of neurological disorders in human subjects, particularly those disorders that originate in the brain.

BACKGROUND OF THE INVENTION

It is well known that in certain patients, epileptic seizures consistently originate from a single location within the brain. When a primary epileptogenic region or seizure focus is suspected some form of monitoring by implanted electrodes may be performed during which time the electrodes are connected to recording instruments such as an electroencephalograph (EEG) machine. Additionally, in some patients, intracranial electrical stimulation using implanted electrodes is performed to map regional brain function as a precursor to surgical removal of the epileptogenic region. During the mapping procedure the stimulation will often induce seizures or seizure-like after discharges from the epileptogenic region.

Electrical stimulation therapy is an alternative to resective surgery. To be most effective in using electrical stimulation as a therapy, the electrode location(s) and electrical pulse parameters must be adapted to each patient. Existing devices for electrical stimulation therapy, such as the Cyberonics NeuroCybernetic Prosthesis System and the Medtronic Activa System, utilize biocalibration methods after the surgical implantation of the therapeutic device. This means that the expense and patient associated risks are incurred before it is known that the device will be therapeutic or how well it will function therapeutically.

SUMMARY OF THE INVENTION

The disclosed invention is a method for determining the optimal electrical stimulation parameters for intracranial stimulation therapy before implantation of a device for electrical stimulation therapy. This method would be used during intracranial electrical stimulation and monitoring procedures which are currently used to identify the epileptogenic region and map regional brain function prior to resective surgery. The present invention method is novel in that unlike prior art methods it is adapted to determine therapeutic stimulation parameters during an evaluation procedure prior to the final implantation of an electrical stimulation device. Such an evaluation procedure would be especially useful for determining the parameters for a closed-loop stimulation device that is responsive to the onset of epileptic seizures such as is described in U.S. Patent No. 6,016,449 to Fischell et al., entitled "SYSTEM FOR TREATMENT OF NEUROLOGICAL DISORDERS."

During standard intracranial electrical stimulation and monitoring procedures, electrical stimulation is applied to one or more of an array of electrodes placed under the patient' s cranium to map the regional brain function to assess the suitability of resective surgery. Seizure-like after discharges or actual clinical seizures can be induced by this stimulation. The reproducibility of such artificially created after discharges makes them ideally suited for use in optimizing electrical stimulation therapy parameters.

The apparatus to perform this method includes an EEG analysis workstation for monitoring the patient's brain and localizing epileptiform activity and an electrical stimulator to both evoke epileptiform activity and provide responsive stimulation therapy. It is envisioned that a multiplicity of electrodes could be used for both the monitoring and localizing and the electrical stimulation aspects of the procedure. The present invention method includes the following steps:

First, during a patient's intracranial electrical stimulation and monitoring procedure, natural epileptiform activity is identified and localized to specific electrodes using the EEG analysis workstation.

Then, manual electrical stimulation is applied to the specific electrodes to induce an after discharge or seizure from the epileptogenic region of the patient's brain. This requires empirical testing of various stimulation parameters until after discharges are evoked.

Stimulation that is identical to that which caused the after discharge is immediately reapplied to the same specific electrodes used in the second step. If the after discharge is

controlled as compared with discharges where no second stimulation is applied, go to the "saving" step below.

If the after discharge is not controlled, adjust the stimulation parameters until it is controlled, then go on to the saving step below. If the after discharge cannot be controlled then the patient may not be a candidate for electrical stimulation therapy.

Save the information on stimulation parameters and specific electrode placement for use in programming the electrical stimulation therapy device and locating the electrode sites.

An additional step of testing the stimulation parameters on naturally occurring seizures can be added. It is also envisioned that an automated system could be used to detect the after discharges and automatically respond rather than having the reapplication of stimulation done manually.

It is also envisioned that with the present invention method the intracranial stimulation electrodes used to respond to the after discharge can be different from the stimulation electrodes used to evoke the after discharge.

It is also envisioned that with the present invention method the period and amplitude of the electrical pulse(s) used to control the after discharge can be different from the period and amplitude of the evoking electrical pulse.

It is also envisioned that with the present invention method the evoking electrical stimulation used to induce the after discharge is first tried at low amplitude and increased in steps until an after discharge is evoked or a threshold is reached.

It is also envisioned that with the present invention method the electrical stimulation used to control the after discharge is first tried at low amplitude and increased in steps until an after discharge is evoked or a threshold is reached.

For the purposes of the present invention a controlled epileptiform discharge is defined as epileptiform activity that has been completely stopped or has had a significant reduction in amplitude or duration as compared to either natural or evoked epileptiform activity.

Thus it is an object of the present invention method to use the patient specific stimulation parameters that successfully control evoked epileptiform activity as the stimulation parameters for an electrical stimulation therapy device used to control natural epileptiform activity.

Another object of the present invention method is to use the specific electrode locations identified during an intracranial electrical stimulation and monitoring procedure as

the electrode locations for an electrical stimulation therapy device to control natural epileptiform activity.

Still another object of the present invention method is to have the intracranial stimulation electrodes used to responsively control evoked epileptiform activity be the same as the stimulation electrodes used to evoke the epileptiform activity.

Still another object of the present invention method is to have the intracranial stimulation electrodes used to responsively control evoked epileptiform activity be different from the stimulation electrodes used to evoke the epileptiform activity.

Yet another object of the present invention method is to have the period and amplitude of the electrical pulse(s) used to control the evoked epileptiform activity be the same as the period and amplitude of the evoking electrical pulse.

Yet another object of the present invention method is to have the period and amplitude of the electrical pulse(s) used to control the evoked epileptiform activity can be different from the period and amplitude of the evoking electrical pulse.

Yet another object of the present invention method is to have the evoking electrical stimulation used to evoke epileptiform activity be first tried at low amplitude and increased in steps until epileptiform activity is evoked or a threshold is reached,

Yet another object of the present invention method is to have the electrical stimulation used to control evoked epileptiform activity be first tried at low amplitude and increased in steps the evoked epileptiform activity is controlled or a threshold is reached.

Yet another object of the present invention method is to have the electrical stimulation used to control natural epileptiform activity be first tried at low amplitude and increased in steps until the natural epileptiform activity is controlled or a threshold is reached.

These and other objects and advantages of this invention will become obvious to a person of ordinary skill in this art upon reading of the detailed description of this invention including the associated drawings as presented herein.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a block diagram of the epileptiform activity monitoring and control system used to determine an optimal set of stimulation parameters to control a patient's epileptic seizures

FIG. 2 is a flowchart of the method showing steps in the method of the present invention used to determine an optimal set of stimulation parameters to control a patient's epileptic seizures.

DETAILED DESCRIPTION OF THE INVENTION

FIG. 1 is a block diagram of the epileptiform activity monitoring and control system 10 used to determine an optimal set of stimulation parameters to control a patient' s epileptic seizures. A multiplicity of depth electrodes 11 are implanted deep into the patient's brain. Intracerebral depth electrodes 11, which are often line arrays of electrodes, are useful for recording from or stimulating deep cerebral structures such as the amygdala, hippocampus, cingulate and orbital-frontal regions which deep cerebral structures are characteristically involved in many medically refractory partial epilepsies.

An array of surface electrodes 12 is placed above the surface of the patient's brain and may contain more than 1 00 electrodes. Brain electrodes 6 include both the depth electrodes 11 and surface electrodes 12 and may also include electrodes placed elsewhere under the patient's scalp near or within the brain.

A multi-strand electrode cable 13 connects the depth electrodes 11 and surface electrodes 12 to a multichannel amplifier 14. After amplification the multiple channels are digitized by an A to D converter 15 and passed on to an EEG analysis workstation 16. The workstation 16 has the capability to process, store, play back and display on a monitor the patient's EEG signals. The workstation 16 may also have the capability to detect epileptiform activity. The multichannel amplifier, A to D converter and EEG analysis workstation together comprise the EEG analysis system 19.

A multichannel electrical stimulator 18 is also connected to the multi-strand cable I 3 allowing selective stimulation on any of the depth electrodes 11 or surface electrodes 12. Although during much of the procedure used to determine an optimal set of stimulation parameters to control a patient's epileptic seizures the stimulator is actuated manually by the physician, the interface 17 also allows the EEG analysis workstation 16 to initiate stimulation. Typical stimulation frequencies are between 20 and 100 Hz and typical stimulation durations are between 0.25 and 5 seconds. Bipolar pulses of duration between 1 and 100 ms with current amplitudes between 0.5 and 15 mA are typical.

Multichannel EEG amplifiers such as the Synamps from NeuroScan, Inc. are commercially available with built in Analog to Digital converters designed to interface to a Windows PC which performs the functions of the EEG analysis workstation 16. EEG analysis and display software is also commercially available to process, store, play back and display on a monitor the patient's EEG signals in real time. Multichannel stimulators are also commercially available and are commonly used by neurologists for brain mapping procedures with implanted deep and/or surface electrodes.

The procedure used to determine an optimal set of stimulation parameters to control a patient's epileptic seizures using the apparatus of FIG. 1 is diagrammed in the flow chart of FIG. 2.

FIG. 2 is a flowchart showing steps in the method 100 of the present invention used to determine an optimal set of stimulation parameters to control a patient's epileptic seizures. The method 100 comprises the following steps:

An implanting electrodes step 5 where a multiplicity of brain electrodes 6 including depth electrodes 11 and surface electrodes 12 as shown in FIG. 1 are implanted. These brain electrodes 6 may be implanted as a two dimensional surface array either epidurally or subdurally or may be a line array placed deep into the brain in sites such as the hippocampus or thalamus.

An EEG data collection step 8 wherein the brain electrodes 6 which best show epileptogenic activity are identified using the EEG analysis workstation 16 of FIG. 1.

An evoking stimulation step 20 wherein stimulation is applied 22 to the electrodes identified in the EEG data collection step 8. Epileptiform activity is looked for 25 and if not found, the stimulation parameters are adjusted 24 and the evoking stimulation re-applied 22 until an epileptiform after discharge or clinical seizure is induced.

A responsive stimulation step 30 wherein evoking stimulation 31 is repeated using the parameters from the evoking stimulation phase 20. When the epileptiform activity begins responsive stimulation 32 is applied with the same stimulation parameters and to the same electrodes that induce the epileptiform activity. Control of the evoked epileptiform activity by the responsive stimulation 32 is looked for 35 and if not found, the responsive stimulation parameters and/or choice of electrodes for applying the responsive stimulation are adjusted 34 and phase 30 is repeated using the modified stimulation parameters. Once epileptiform activity control is detected by process 35, the responsive stimulation parameters comprising amplitude, frequency, duty cycle and choice of stimulation electrodes are saved 36.

The patient is now ready for the natural epileptiform activity control step 40. The system 100 of FIG. 1 is used to monitor EEG activity looking for natural epileptiform activity 41 . When it is detected, responsive stimulation 42 is applied using the parameters saved 36 from the responsive stimulation step 30. Control of the natural epileptiform activity by the responsive stimulation 42 is looked for 45 and if not found, the responsive stimulation parameters and/or choice of electrodes for applying the responsive stimulation are adjusted 44 and phase 40 is repeated using the modified stimulation parameters. Once natural epileptiform activity control is detected by the process 45, the responsive stimulation parameters comprising amplitude, frequency, duty cycle and choice of stimulation electrodes are saved in step 50.

The parameters saved in step 50 could then be used to program an implantable neurostimulator for the treatment of epileptiform activity with electrical stimulation.

The evoking stimulation 22 and 31 can be applied to any one, several, or all electrodes of the multiple brain electrodes 6 of FIG. 1. The responsive stimulation 32 and 42 can be applied to any one, several, or all electrodes of the multiple brain electrodes 6 of FIG. 1. The evoking stimulation 22 and 31 sent to each responsive electrode can be programmed to be identical or different from one another in amplitude, frequency, waveform, phase duration, or time duration. The responsive stimulation signals 32 and 42 sent to each responsive electrode can be identical to or they can be programmed to be identical or different from one another in amplitude, frequency, waveform, phase duration, or time duration.

The responsive stimulation 32 and 42 sent to each responsive electrode can be identical to the evoking stimulation 22 and 31 or they can differ in any stimulation parameter.

Examples of the iterative methods for incremental stimulation increases for each of the steps 20, 30 and 40 are described below.

In the evoking stimulation step 20, the evoking stimulation 22 can first be applied at a low amplitude such as 0.5 mA and the epileptiform activity looked for 25. If no evoked epileptiform activity occurs, the stimulation parameters are adjusted 24 such that the amplitude is increased by a increment such as 0.5 mA and the evoking stimulation is reapplied 22. With each iteration where control does not occur, the amplitude is increased by the 0. 5 mA increment 44 until the epileptiform activity is evoked or a threshold such as 15 mA is reached.

In the stimulation step 30, the responsive stimulation 32 can first be applied at a low amplitude such as 0.5 mA and the control of evoked epileptiform activity looked for 35. If no

control of the evoked epileptiform activity occurs, the stimulation parameters are adjusted 34 such that the amplitude is increased by a increment such as 0.5 mA and the responsive stimulation is reapplied 32. With each iteration where control does not occur, the amplitude is increased by the 0.5 mA increment 44 until the evoked epileptiform activity is controlled or a threshold such as 15 mA is reached.

In the natural epileptiform activity control step 40, the responsive stimulation 42 can first be applied at a low amplitude such as 0.5 mA and the control of natural epileptiform activity looked for 45 . If no control of the natural epileptiform activity occurs, the stimulation parameters are adjusted 44 such that the amplitude is increased by a increment such as 0.5 mA and the responsive stimulation is reapplied 42 when the next natural epileptiform activity occurs 41 . With each iteration where control does not occur, the amplitude is increased by the 0. 5 mA increment 44 until the natural epileptiform activity is controlled or a threshold such as 15 mA is reached.

Various other modifications, adaptations, and alternative designs are of course possible in light of the above teachings. Therefore, it should be understood at this time that within the scope of the appended claims the invention might be practiced otherwise than as specifically described herein.

What is claimed is:

1. A method of selecting electrical stimulation parameters to control epileptiform activity, comprising the steps of:

implanting a sub-cranial brain electrode and connecting the brain electrode to an EEG analysis system;

collecting and analyzing EEG signals from the brain electrode with the EEG analysis system to identify whether the electrode is at or near an epileptogenic focus of the patient;

connecting the brain electrodes to an electrical stimulator, the electrical stimulator being programmable with respect to at least one stimulation parameter;

applying an evoking electrical stimulation signal from the electrical stimulator to the brain electrode;

adjusting the stimulation parameter and repeating the applying step until evoked epileptiform activity is present in the EEG signals; and

reapplying the evoking electrical stimulation signal that caused evoked epileptiform activity to be present; and

immediately applying a responsive electrical stimulation signal to control the epileptiform activity.

2. A method of selecting electrical stimulation parameters to control epileptiform activity, comprising the steps of:

identifying epileptiform activity in an EEG signal received with a sub-cranial brain electrode and analyzed by an EEG analysis system;

applying a responsive electrical stimulation signal with a stimulator to control the epileptiform activity, wherein the stimulator has an adjustable stimulation parameter; and

adjusting the stimulation parameter and repeating the applying step the epileptiform activity is terminated.

3. A system for selecting electrical stimulation parameters to control epileptiform activity, the system comprising:

an implanted brain lead having at least one electrode, wherein the implanted brain lead is adapted to receive an EEG signal from a patient's brain and to provide an electrical stimulation signal to the patient's brain;

an EEG signal analysis system including a display workstation; and

a stimulator adapted to provide responsive electrical stimulation to the patient, wherein the stimulator has at least one adjustable stimulation parameter;

wherein the adjustable stimulation parameter is adapted to be adjusted in response to an indication from the EEG signal analysis system representative of epileptiform activity in the EEG signal.

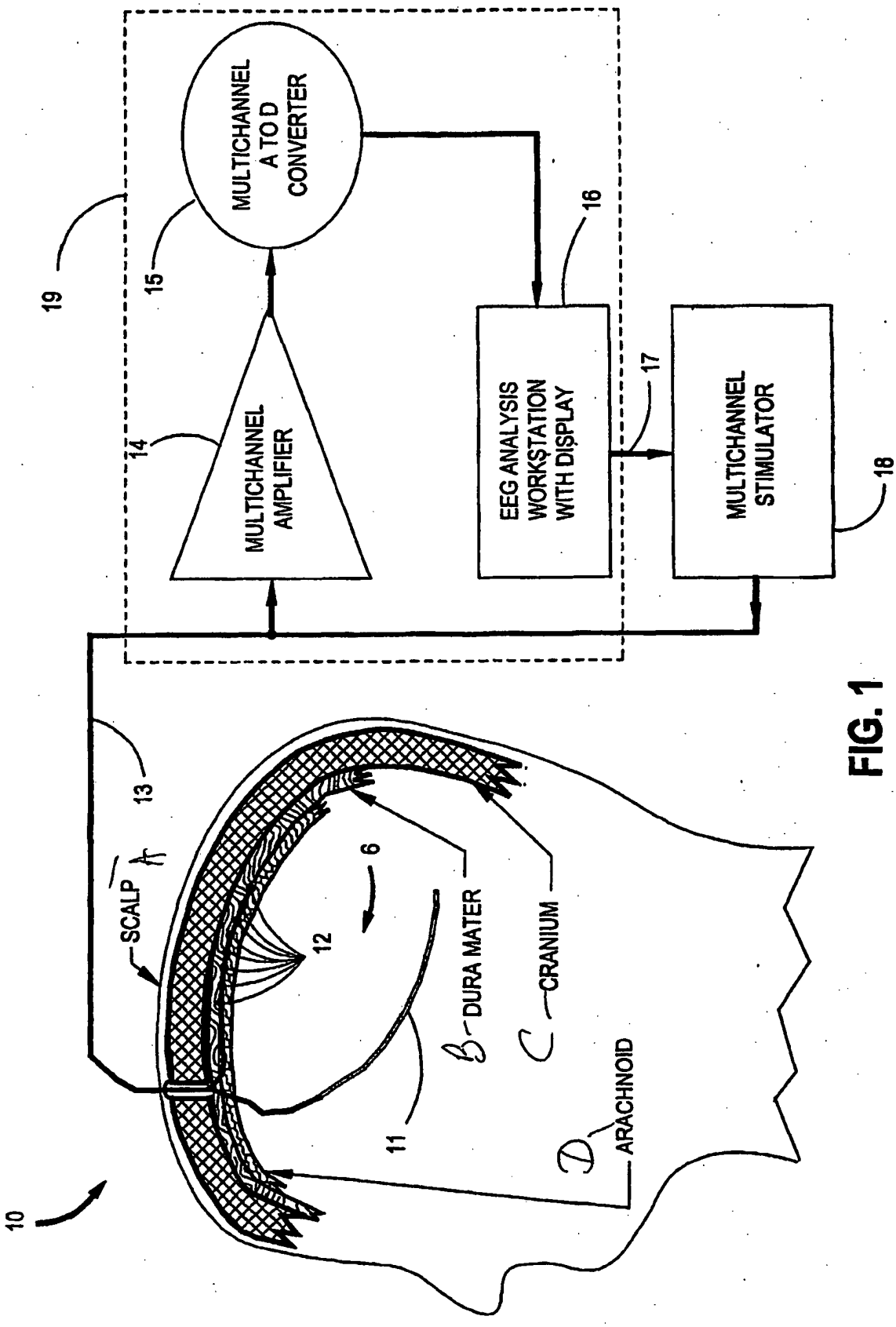

MULTICHANNEL A TO D CONVERTER
MULTICHANNEL AMPLIFIER
EEG ANALYSIS WORKSTATION WITH DISPLAY
MULTICHANNEL STIMULATOR
19
15
14
16
17
18
13
10
SCALP
12
6
DURA MATER
CRANIUM
ARACHNOID
11
A
B
C
D

FIG. 1

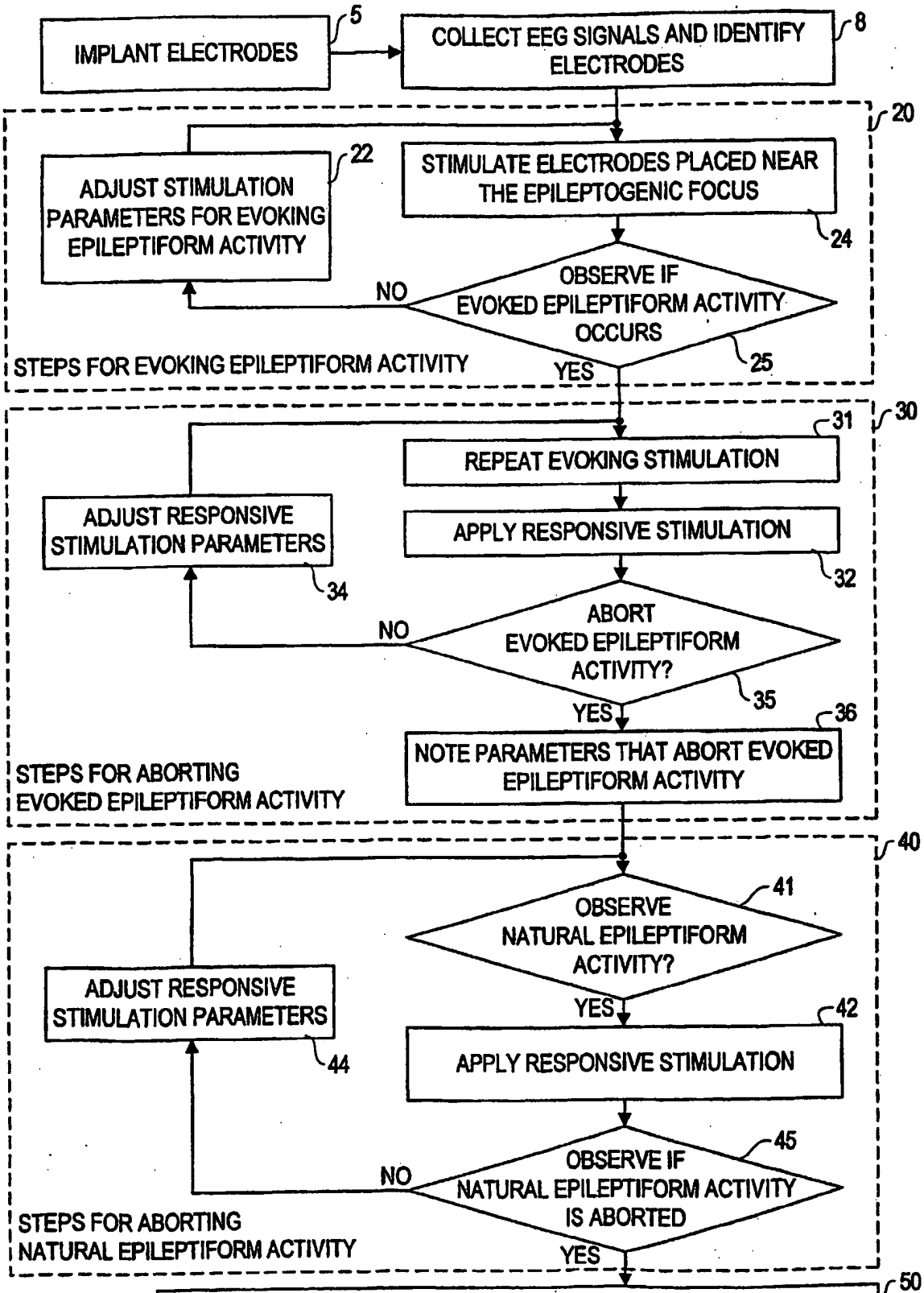

IMPLANT ELECTRODES
5
COLLECT EEG SIGNALS AND IDENTIFY ELECTRODES
8
20
ADJUST STIMULATION PARAMETERS FOR EVOKING EPILEPTIFORM ACTIVITY
22
STIMULATE ELECTRODES PLACED NEAR THE EPILEPTOGENIC FOCUS
24
OBSERVE IF EVOKED EPILEPTIFORM ACTIVITY OCCURS
25
NO
YES
STEPS FOR EVOKING EPILEPTIFORM ACTIVITY
30
31
REPEAT EVOKING STIMULATION
ADJUST RESPONSIVE STIMULATION PARAMETERS
34
APPLY RESPONSIVE STIMULATION
32
ABORT EVOKED EPILEPTIFORM ACTIVITY?
35
NO
YES
36
NOTE PARAMETERS THAT ABORT EVOKED EPILEPTIFORM ACTIVITY
STEPS FOR ABORTING EVOKED EPILEPTIFORM ACTIVITY
40
41
OBSERVE NATURAL EPILEPTIFORM ACTIVITY?
ADJUST RESPONSIVE STIMULATION PARAMETERS
44
YES
42
APPLY RESPONSIVE STIMULATION
45
OBSERVE IF NATURAL EPILEPTIFORM ACTIVITY IS ABORTED
NO
YES
STEPS FOR ABORTING NATURAL EPILEPTIFORM ACTIVITY
50
SAVE ELECTRICAL STIMULATION PARAMETERS THAT ABORT NATURAL EPILEPTIFORM ACTIVITY FOR PROGRAMMING AN IMPLANTABLE DEVICE

FIG. 2

User: pics8
Host: pgpubt50
Class:
Job: pics_pct_hp2-108

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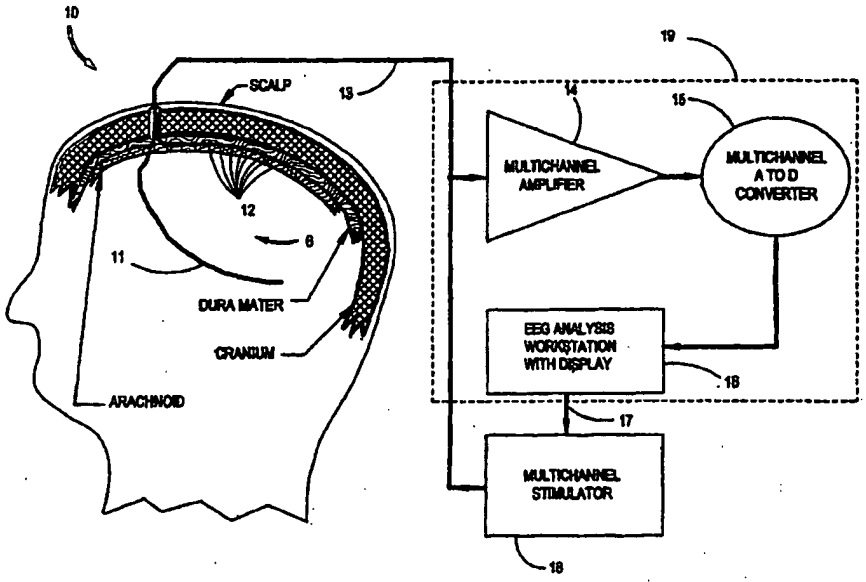

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61N1/36 A61B5/0476

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61N A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 066 163 A (JOHN MICHAEL SASHA) 23 May 2000 (2000-05-23) the whole document	3
X	US 3 850 161 A (LISS S) 26 November 1974 (1974-11-26) the whole document	3
Y	US 6 016 449 A (UPTON ADRIAN R M ET AL) 18 January 2000 (2000-01-18) cited in the application the whole document	3
Y	US 5 797 965 A (DITTO WILLIAM L ET AL) 25 August 1998 (1998-08-25) the whole document	3

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 August 2003	03/09/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Ferrigno, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/41704

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1 2
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy and surgery

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/41704

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